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**Abstract:** AIMS Mortality after cardiac resynchronization therapy (CRT) is difficult to predict. We sought to design and validate a simple prognostic score for patients implanted with CRT, based on readily available clinical variables, including age, gender, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, presence/absence of atrial fibrillation, presence/absence of atrioventricular junction ablation, coronary heart disease, diabetes, and implantation of a CRT device with defibrillation. **METHODS** For predictive modelling, 5153 consecutive patients enrolled in 72 European centres (79% male; LVEF  $25.9 \pm 6.85\%$ ; NYHA class III-IV 77.5%; QRS  $158.4 \pm 32.3$  ms) were randomly split into derivation (70%) and validation (30%) samples. The primary endpoint was total mortality and the secondary endpoint was cardiovascular mortality. The final predictive model fit was assessed by plotting observed vs. predicted survival. **RESULTS** In the entire cohort, 1004 deaths occurred over a follow-up of 14 409 person years. Total mortality ranged from 3.1% to 28.2% at 2 years in the first and fifth quintile of the risk score, respectively. At 5 years, total mortality was 10.3%, 18.6%, 27.6%, 36.1%, and 58.8%, from the first to the fifth quintile. Compared with the lowest quintile (Q), total mortality was significantly higher in the other four quintiles [Q2 hazard ratio (HR) = 1.71; Q3 HR = 2.20; Q4 HR = 4.03; Q5 HR = 8.03; all  $P < 0.001$ ]. The final model, which was based on the entire cohort using the above variables, showed a good discrimination (Harrell's  $c = 0.70$ ) and high explained variation (0.26). The mean predicted survival fitted well with the observed survival for up to 6 years of follow-up. **CONCLUSIONS** The VALID-CRT risk score, which is based on routine, readily available clinical variables, reliably predicted the long-term total and cardiovascular mortality in patients undergoing CRT. While this score cannot be used to predict the benefit of CRT, it may be useful for predicting survival after CRT. This may have useful implications for follow-up.

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# Validation of a simple risk stratification tool for patients implanted with Cardiac Resynchronization Therapy: the VALID-CRT risk score

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|--------------------|---|
| <b>Aims</b>        | Mortality after cardiac resynchronization therapy (CRT) is difficult to predict. We sought to design and validate a simple prognostic score for patients implanted with CRT, based on readily available clinical variables, including age, gender, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, presence/absence of atrial fibrillation, presence/absence of atrioventricular junction ablation, coronary heart disease, diabetes, and implantation of a CRT device with defibrillation.   |
| <b>Methods</b>     | For predictive modelling, 5153 consecutive patients enrolled in 72 European centres (79% male; LVEF $25.9 \pm 6.85\%$ ; NYHA class III–IV 77.5%; QRS $158.4 \pm 32.3$ ms) were randomly split into derivation (70%) and validation (30%) samples. The primary endpoint was total mortality and the secondary endpoint was cardiovascular mortality. The final predictive model fit was assessed by plotting observed vs. predicted survival.  |
| <b>Results</b>     | In the entire cohort, 1004 deaths occurred over a follow-up of 14 409 person years. Total mortality ranged from 3.1% to 28.2% at 2 years in the first and fifth quintile of the risk score, respectively. At 5 years, total mortality was 10.3%, 18.6%, 27.6%, 36.1%, and 58.8%, from the first to the fifth quintile. Compared with the lowest quintile (Q), total mortality was significantly higher in the other four quintiles [Q2 hazard ratio (HR) = 1.71; Q3 HR = 2.20; Q4 HR = 4.03; Q5 HR = 8.03; all $P < 0.001$ ]. The final model, which was based on the entire cohort using the above variables, showed a good discrimination (Harrell's $c = 0.70$ ) and high explained variation (0.26). The mean predicted survival fitted well with the observed survival for up to 6 years of follow-up. |
| <b>Conclusions</b> | The VALID-CRT risk score, which is based on routine, readily available clinical variables, reliably predicted the long-term total and cardiovascular mortality in patients undergoing CRT. While this score cannot be used to predict the benefit of CRT, it may be useful for predicting survival after CRT. This may have useful implications for follow-up.  |
| <b>Keywords</b>    | Risk-stratification • Cardiac resynchronization therapy • Heart failure • Prognostic index  |

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## Introduction

Cardiac resynchronization therapy (CRT) is a standard therapy for patients with systolic heart failure (HF) and a prolonged QRS duration.<sup>1–3</sup> Although the treatment effect of this therapy is superior to many others, the recognition of a variable outcome has prompted efforts in risk-stratifying patients on the basis of pre-implant assessments. Mechanical dyssynchrony measured by echocardiography initially held promise as a predictor of outcome after CRT.<sup>4–6</sup> However, these measures have not stood the test of a multicentre trial such as PROSPECT,<sup>4</sup> in which no echocardiographic measure of mechanical dyssynchrony proved to be useful in predicting the response to CRT. Other imaging variables, such as scar burden<sup>7,8</sup> and scar location<sup>8,9</sup> on cardiovascular magnetic resonance have also been shown to predict the outcome of CRT. Importantly, however, such measures have not been validated in multicentre studies.

An accepted prognostic model for predicting survival in HF patients is the Seattle Heart Failure Model (SHFM).<sup>10</sup> Although it takes into account the eventual use of CRT or implantable cardioverter defibrillator (ICD) therapy, it was not specifically designed for patients with HF who have already undergone CRT device implantation. This, together with the fact that it requires quantification of 25 variables, makes it unreliable and impracticable. In contrast, relatively simple risk stratification systems, such as the Euroscore used in cardiothoracic surgery,<sup>11</sup> may seem simplistic in terms of the few variables used, have nevertheless been adopted worldwide. Similarly, the field of CRT demands a simple risk-stratification algorithm based on few variables that are routinely available. In this study, we hypothesized that the long-term mortality following CRT device implantation can be predicted using a simple algorithm based on readily available clinical variables. We have externally validated the utility of a simple predictive model based on 'real-world' patients undergoing CRT.

## Methods

This was a prospective, multicentre, international, longitudinal, observational study including consecutive patients undergoing CRT in the period from May 1999 to February 2012 in 72 European centres (from Italy, Switzerland, France, Germany, and England). This collaboration arose from another larger experience, which comprised 95 centres in Europe.<sup>12</sup> The centres involved in the present study were those that had systematically collected the data considered in this study. In order to fit a prediction model for time to total and cardiovascular death, variables that have previously been found to predict mortality in other studies were considered. These included age, gender, ICD back up, atrial fibrillation, presence or absence of atrioventricular junction ablation (AVJA) in the case of atrial fibrillation, ischaemic aetiology, diabetes, New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), QRS duration and morphology, left ventricular (LV) lead position, and creatinine.<sup>1,2,13–18</sup> Although data collection was prospective, the present analysis was retrospective. Data collection and analysis were approved by the individual sites' Institutional Review Board or Clinical Ethics Committee. The study conformed to the Declaration of Helsinki. All patients gave written, informed consent for data collection and analysis.

## Patient population

Inclusion criteria were: systolic HF in NYHA class III or ambulatory IV (or II in the case of a recent hospitalization because of HF), LVEF  $\leq 35\%$  and QRS  $\geq 120$  ms, despite maximum tolerated pharmacological therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor-blockers, beta-adrenergic blockers, diuretics, and spironolactone for at least 2 months. A clinical diagnosis of HF was made on the basis of documented evidence of systolic dysfunction on echocardiography. A diagnosis of ischaemic cardiomyopathy was made if systolic dysfunction was associated with a history of myocardial infarction and/or if there was angiographically significant coronary heart disease. Exclusion criteria were: contraindications to cardiac pacing; myocardial infarction or acute coronary syndrome within the previous 3 months; severe structural valvular heart disease; and the presence of co-morbidities likely to curtail survival to 12 months or less.

## Device therapy

Transvenous CRT-pacing (CRT-P) or CRT-defibrillation (CRT-D) device implantation was undertaken using standard transvenous techniques under local anaesthesia. A lateral or posterolateral LV site was considered optimal for LV lead by most implanters. In patients with sinus rhythm, the CRT device was programmed in atrial-synchronous sequential pacing. Atrioventricular optimization was undertaken within 24 h of device implantation and at 6 months, using Doppler echocardiography and the iterative method.<sup>19</sup> In patients with atrial fibrillation, the minimum heart rate was set at  $\geq 70$  bpm and the maximum rate was set at 70% of the theoretical maximum heart rate. A rate-adaptive response was activated both in atrial fibrillation (AF) patients with and without AVJA.

## Endpoints

The primary endpoint was total mortality and the secondary endpoint was cardiovascular mortality. Patients undergoing left ventricular assist device implantation or urgent heart transplantation were classified as cardiac deaths. Mortality data was collected through medical records, and where appropriate, from interviews with patient's carers.

## Statistical analysis

Data were described as mean and standard deviation (SD) if continuous and as counts and per cent in the case of categorical variables. For model building, the cohort was randomly split into a testing and a validating sample, encompassing 70% and 30% of patients, respectively. In order to fit a prediction model for time to total and cardiovascular death, the following baseline predictors were considered: age, gender, ICD back-up, atrial fibrillation, presence or absence of AVJA in case of atrial fibrillation, ischaemic aetiology, diabetes, NYHA, LVEF, QRS duration and morphology, LV lead position, and creatinine. Pharmacological treatment was not considered, as the choice and dosage is strictly based on clinical indication, which in turn is measured by the other variables. In order to retain a sufficient number of subjects in the analysis, we only considered variables with missing data below 25%. The missing mechanism was considered at random. All variables were considered as candidate predictors; those with  $P < 0.1$  at the univariable analysis were included in the model. Creatinine and natriuretic peptides were not included in the model because of missing data ( $>25\%$ ). Flexible Royston–Parmar models<sup>20</sup> were fitted to the testing

**Table 1** Characteristics of the study group

| Variable          | Derivation (N = 3629) |       |       | Validation (N = 1524) |       |       | All (N = 5153) |       |       |
|-------------------|-----------------------|-------|-------|-----------------------|-------|-------|----------------|-------|-------|
|                   | n                     | Mean  | SD    | n                     | Mean  | SD    | n              | Mean  | SD    |
| Age (years)       | 3629                  | 66.27 | 10.15 | 1524                  | 66.39 | 10.15 | 5153           | 66.31 | 10.15 |
| QRS duration (ms) | 3629                  | 158.4 | 32.3  | 1524                  | 157.7 | 32.4  | 5153           | 158.2 | 32.3  |
| LVEF (%)          | 3629                  | 25.87 | 6.85  | 1524                  | 25.84 | 6.72  | 5153           | 25.86 | 6.81  |
|                   |                       | %     |       |                       | %     |       |                | %     |       |
| Sinus rhythm      | 3007                  | 82.86 |       | 1257                  | 82.48 |       | 4264           | 82.75 |       |
| AF + drugs        | 387                   | 10.66 |       | 163                   | 10.7  |       | 550            | 10.67 |       |
| AF + AVJA         | 235                   | 6.48  |       | 104                   | 6.82  |       | 339            | 6.58  |       |
| CRT-D             | 2740                  | 75.5  |       | 1159                  | 76.05 |       | 3899           | 75.66 |       |
| Male gender       | 2845                  | 78.4  |       | 1192                  | 78.22 |       | 4037           | 78.34 |       |
| CAD               | 1618                  | 44.59 |       | 679                   | 44.55 |       | 2297           | 44.58 |       |
| NYHA III–IV       | 2812                  | 77.49 |       | 1182                  | 77.56 |       | 3994           | 77.51 |       |
| Diabetes          | 904                   | 24.91 |       | 370                   | 24.28 |       | 1274           | 24.72 |       |
| LBBB              | 2438                  | 89.0  |       | 1003                  | 89.3  |       | 3441           | 89.1  |       |
| LV lead L/PL      | 1888                  | 84.2  |       | 773                   | 83.3  |       | 2661           | 83.6  |       |

LVEF, left ventricular ejection fraction; AF, atrial fibrillation; AVJA, atrioventricular junction ablation; CAD, coronary artery disease; CRT-D, cardiac resynchronization defibrillation; NYHA, New York Heart Association; LBBB, left bundle branch block; L/PL, lateral or posterolateral LV position.

sample and the Weibull model was chosen as the more appropriate, based on the Akaike information criterion. Linearity was checked and proven for all continuous variables. Furthermore, continuous variables were centred on the mean to draw plots of predicted survival. This model was fitted in the testing sample; discrimination was assessed on both the testing and validating samples. To this end, we created four prognostic groups for all patients using cutpoints at the 15th, 50th, and 85th centiles of the prognostic index (the linear combination of predictors and their coefficients). These centiles approximated well to the Cox cut points,<sup>21</sup> thus minimizing the loss of information when discretizing a normally distributed continuous variable into a given number of groups. We then plotted Kaplan–Meier curves for the two samples to assess discrimination graphically. Finally, both samples were combined and the model was fitted again to derive the algorithm for computation of the predictor index. The final model fit was assessed by plotting observed and mean survival. The model Royston's explained variation and model Harrell's *c* for discrimination were also computed. The predictor index was then categorized into quintiles of its distribution to obtain groups at increasing risks of death and the corresponding survival curves were plotted to allow derivation of the probability of survival at each time-point at a given risk category.<sup>20–22</sup> Stata 13.1 (StataCorp, College Station, TX, USA) was used for statistical analysis. A two-sided *P*-value < 0.05 was considered statistically significant.

## Results

The study included 5153 patients with a median follow up of 39 months (Table 1) [age  $66.3 \pm 10.5$  years (mean  $\pm$  SD), 79% men, 77% in NYHA III–IV, mean QRS  $158 \pm 32$  ms, 88% with left bundle branch block (LBBB), LVEF  $25.9 \pm 6.8\%$ , 25% prevalence of diabetes, 17% atrial fibrillation, 84% with a lateral or posterolateral LV lead position, and 76% implanted with an ICD back up). Patients implanted with CRT were on optimized drug therapy: 85% were treated with angiotensin-converting enzyme (ACE)-inhibitors or angiotensin receptor blockers, 80% with beta-blockers, 54% with

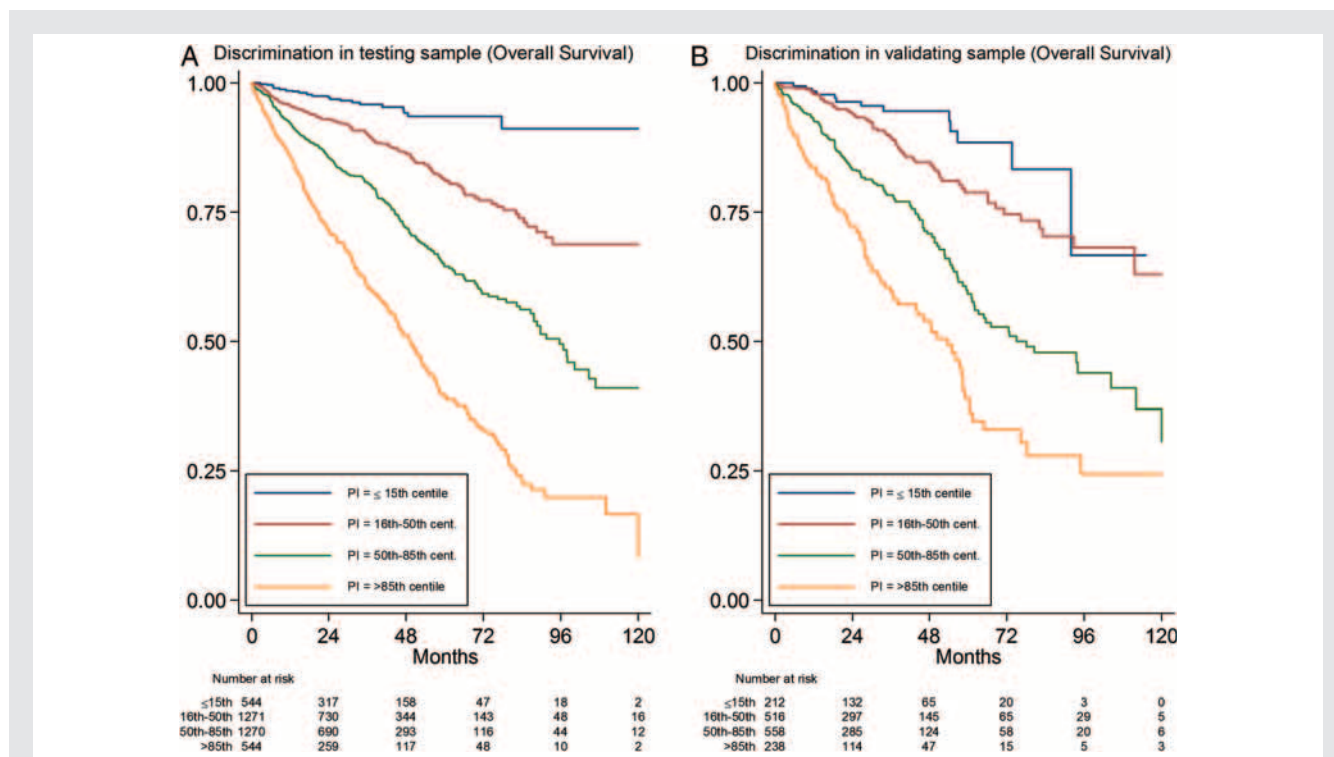
spironolactone, 92% loop diuretics, 37% amiodarone, and 24% treated with digoxin. Drug therapy and baseline characteristics were similar in the derivation and validation samples. Over 14 409 person years of follow-up there were 1004 deaths.

## Model construction

First, a parametric Weibull model was fitted in the testing sample of 3629 patients. Kaplan–Meier curves, constructed from four predefined risk groups of the prognostic index, showed a good discrimination, with perfect separation of the curves for the derivation sample, which was maintained with acceptable approximation to the validation sample (Figure 1). Given the good discrimination of the tentative model in both the derivation and validation samples, data were collapsed and a final Weibull parametric model was constructed on the entire cohort of 5133 patients. As shown in Table 2, the risk of cardiovascular death was highest with advancing age, a lower LVEF, AF without AVJA, male gender, ischemic aetiology, a higher NYHA class (III and IV), and no ICD back up. Importantly, QRS morphology and duration as well as LV lead location emerged as non-significant predictors on univariable analyses ( $P > 0.5$ ) and dropped from the model. An algorithm to compute the predictor index was derived from the model and, based on the quintiles of its distribution, five groups of increasing risks were defined (Table 3 and Figure 2). The cumulative probability of dying at 2 years and 5 years is also reported for each risk group, with an almost linear increase in risk for the first four groups and a major increase for the fifth group at both 2 years and 5 years.

## Model validation

The model showed good discrimination (Harrell's *c* = 0.70) and high explained variation (EV = 0.26). In addition, the mean survival,



**Figure 1** Overall survival based on the prognostic index (PI). (a) discrimination ability of the prognostic model built in the testing sample. Kaplan–Meier curves correspond to four groups built from the prognostic index (linear combination of predictors and their coefficients) with predefined cut-offs. (b) the same prognostic index has been computed over the validating sample and Kaplan–Meier curves have been plotted similarly.

**Table 2 Multivariable Weibull prognostic model for death from any cause**

| Predictor*     | HR   | 95% CI    | P      |
|----------------|------|-----------|--------|
| Age, yrs       | 1.03 | 1.02–1.03 | <0.001 |
| LVEF (%)       | 0.96 | 0.95–0.97 | <0.001 |
| SR             | 1.00 |           |        |
| AF + drugs     | 1.90 | 1.60–2.26 | <0.001 |
| AF + AVJAb     | 0.86 | 0.69–1.08 | 0.195  |
| CRT-D (yesb)   | 0.52 | 0.45–0.59 | <0.001 |
| Gender (male)  | 1.50 | 1.26–1.78 | <0.001 |
| CAD (yes)      | 1.37 | 1.20–1.57 | 0.015  |
| NYHA (III–IV)  | 2.32 | 1.85–2.90 | <0.001 |
| Diabetes (yes) | 1.19 | 1.00–1.41 | 0.049  |

HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; SR, sinus rhythm; AF, atrial fibrillation; AVJA, atrioventricular junction ablation; CRT-D, cardiac resynchronization defibrillation; CAD, coronary artery disease; NYHA, New York Heart Association.

\*Test for AF:  $p < 0.001$ ; AF + AVJA vs. AF + drugs: HR 0.45, 95% CI 0.35–0.59,  $P < 0.001$ .

Model  $P$ -value  $< 0.001$ ; Royston explained variation 0.26, Harrell's  $c = 0.70$ .

Abbreviations as in Table 1

as predicted by the model fitted well the observed survival, as shown by the Kaplan–Meier curves (Figure 2). In the lowest risk group, however, the predicted survival after 6 years of follow-up tended to be better than the observed survival. A good fit was

observed to all other groups over the entire follow-up period. Finally, when plotting the mean survival according to deciles of the prognostic index, a good separation of curves emerged throughout the range of values and time, confirming the good predictive ability of the model. The model is:

**Valid CRT score  $PI = 0.028 \times \text{age } 66 - 0.044 \times \text{LVEF}25 + 0.646 \times \text{AF}1 - 0.154 \times \text{AF}2 - 0.656 \times \text{ICD} + 0.405 \times \text{GENDER} + 0.317 \times \text{CAD} + 0.844 \times \text{NYHA}34 + 0.167 \times \text{diabetes}$**

where:

age66 = age – 66 years;

LVEF = LVEF – 25;

AF1 = 1 if AF without AVJA is present, 0 otherwise (meaning both sinus rhythm or AF+AVJA);

AF2 = 1 if AF with AVJA is present, 0 otherwise (meaning both sinus rhythm or AF without AVJA);

ICD, CAD, NYHA III–IV, diabetes = 1 if present, 0 otherwise;

gender = 1 if male, 0 if female.

Renal function data were missing in a consistent part of the cohort, consequently, this datum could not be included, per protocol, into the main model (figure 3). Nonetheless, we decided, to perform a second predictive model in the subgroup of patients presenting baseline creatinine values. Owing to the lower number of patients included in this second model, this subgroup was divided in three tertiles. As reported in the Supplementary material online (Figure S1 and Table S1), even when creatinine was included, the predicted and the validated survival curves remained perfectly



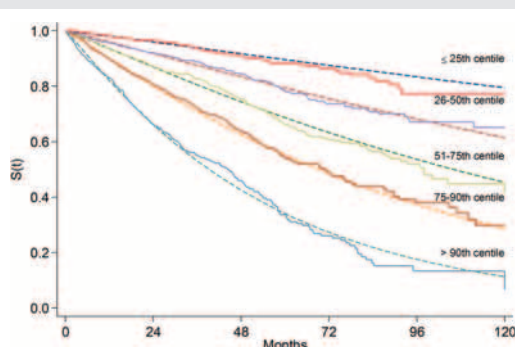
**Table 3** Algorithm for calculating the prognostic index (PI) and classifying patients in the pertinent risk groups\*

| Quintiles of PI | PI min | PI max | 2-year mortality, % (95% CI) | 5-year mortality, % (95%CI) | HR (95% CI)       | Model P |
|-----------------|--------|--------|------------------------------|-----------------------------|-------------------|---------|
| Risk group 1    | −1.841 | 0.061  | 3.1 (2.1–4.5)                | 10.3 (7.8–13.6)             | 1.00              |         |
| Risk group 2    | 0.062  | 0.558  | 5.9 (4.5–7.7)                | 18.6 (15.2–22.7)            | 1.71 (1.26–2.33)  | 0.001   |
| Risk group 3    | 0.559  | 0.937  | 10.9 (9.0–13.3)              | 27.6 (23.5–32.3)            | 2.20 (2.10–3.33)  | <0.001  |
| Risk group 4    | 0.938  | 1.364  | 13.9 (11.7–16.4)             | 36.1 (31.6–41.2)            | 4.03 (3.06–5.32)  | <0.001  |
| Risk group 5    | 1.365  | 3.157  | 28.2 (25.3–31.4)             | 58.8 (54.4–63.2)            | 8.03 (6.18–10.45) | <0.001  |

CI, confidence interval; HR, hazard ratio.

The model is: **Valid cardiac resynchronization therapy (CRT) score**  $PI = 0.028 \times \text{age66} - 0.044 \times \text{LVEF25} + 0.646 \times \text{AF1} - 0.154 \times \text{AF2} - 0.656 \times \text{ICD} + 0.405 \times \text{GENDER} + 0.317 \times \text{CAD} + 0.844 \times \text{NYHA34} + 0.167 \times \text{diabetes}$

where: age66 = age – 66 years; LVEF = left ventricular ejection fraction – 25; AF1 = 1 if atrial fibrillation (AF) without atrioventricular junction ablation (AVJA) is present; 0 otherwise (meaning both sinus rhythm or AF + AVJA); AF2 = 1 if AF with AVJA is present, 0 otherwise (meaning both sinus rhythm or AF without AVJA); ICD, ; CAD, coronary artery disease; New York Heart Association (NYHA) III–IV, diabetes = 1 if present, 0 otherwise; gender = 1 if male, 0 if female.



**Figure 2** Observed and mean overall survival. Observed and mean overall survival according to the quintiles of the predictor index distribution; jagged lines correspond to the observed survival, while the dashed lines correspond to the mean survival as computed from the parametric model.

superimposed, thus reinforcing the goodness of the predictive model.

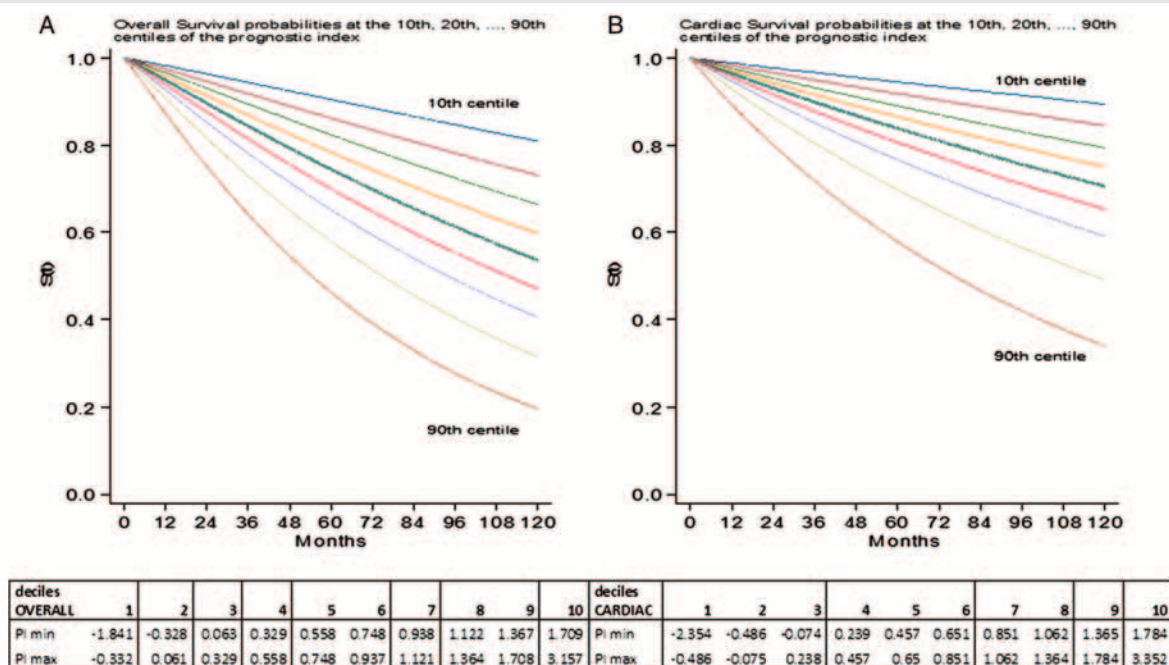
## Discussion

In this study, we have shown that the VALID-CRT risk score, which is based on a simple risk-stratification algorithm, reliably predicts total and cardiovascular mortality after CRT. Importantly, the score comprises nine variables that are readily available in clinical practice and which have also been found to relate to a poor outcome in other studies.<sup>1,2,13–18</sup> On external validation, the predictive model is reliable for up to 6 years of follow-up following CRT device implantation. As we have no control group, this score should not be employed to assess the survival benefit of CRT, but rather absolute survival in patients after CRT device implantation. The score may be of value in tailoring follow-up and treatment strategies in clinical practice. In addition, this score may be useful in selecting patients with specific risk profiles into clinical trials.

Several studies have shown that QRS duration before implantation relates to a survival benefit from CRT. A meta-analysis of individual patient data from major CRT trials confirms a survival benefit

at a QRS >140 ms and less certain prognostic benefit between 120 and 140 ms.<sup>23</sup> In a *post hoc* analysis of REVERSE,<sup>24</sup> there was a linear relationship between clinical response and QRS durations, starting at 120 ms. In addition, QRS morphology also relates to survival benefit of CRT. A *post hoc* analyses of MADIT-CRT suggested a reduced benefit in patients with non-LBBB QRS morphology.<sup>25</sup> A meta-analysis of individual data from 3782 patients recruited in landmark CRT trials, showed that while QRS duration was an independent predictor of outcome after CRT, LBBB morphology was not.<sup>23</sup> This raises the possibility that the reduced benefit in non-LBBB patients may relate to a shorter QRS duration rather than to QRS morphology *per se*.

In this study, neither QRS duration nor morphology predicted absolute survival after CRT. This, however, could be at least partially due to the fact that almost 90% of patients had a QRS >130 ms and a LBBB. Echocardiographic measures of mechanical dyssynchrony assessed before CRT device implantation have been extensively studied as possible predictors of the response to and outcome of CRT.<sup>26–30</sup> In the multicentre PROSPECT study, however, no echocardiographic measure of mechanical dyssynchrony proved to be useful in predicting response to CRT.<sup>4</sup> Factors other than measures of mechanical dyssynchrony have also been explored as potential predictors. These include age, gender, NYHA class, HF aetiology, atrial rhythm, QRS duration and morphology, LV lead position, renal impairment, and biomarkers, such as natriuretic peptides<sup>13,26,27</sup>. As with echocardiography, studies on these potential predictors of response to and survival benefit after CRT have generally focused on one chosen factor without consideration of other factors. Sample sizes have usually been small and the follow-up period generally short (up to 6 months). Moreover, most studies have used surrogates of outcome, such as LV reverse remodelling. Almost without exception, potential predictors have not been externally validated by different centres in different countries. An algorithm based on pre-implant variables, such as gender, heart failure aetiology, QRS complex morphology, LV volume and left atrial volume was tested by Goldenberg *et al.*<sup>31</sup> in the MADIT-CRT study, but the follow-up was limited to 2.4 years. A score consisting of a measure of dyssynchrony obtained from cardiovascular magnetic resonance, location of myocardial scar and creatinine has also been explored.<sup>32</sup> However, this score involves



**Figure 3** Overall and cardiovascular mean survival and classification of patients into deciles of the predictive index (PI). In practical use, once the PI has been computed for any given patients with the provided algorithm and classified in any of the 10 risk groups based on deciles, cardiac (a) and overall (b) survival at any time can be read from the graph.

undertaking a cardiac magnetic resonance scan, which may not be available in some centres. Moreover, the score has not been externally validated. The SHFM is a multifactorial model that predicts mortality in patients with HF. The score has been validated in randomized controlled trials and in community practice settings in the USA and in Europe.<sup>10,33</sup> The model has also been applied to CRT trials, such as COMPANION<sup>1</sup> and CARE-HF<sup>2</sup> and takes into account post-implant variables, such as device modality (CRT-P or CRT-D). However, the follow-up in this validation is limited to 12 months and 29.4 months, respectively. In a recent multicentre external validation in patients undergoing CRT, the SHFM provided only a modest predictive ability to predict survival.<sup>34</sup> In contrast, the VALID-CRT score, as presented herein, provides a good discrimination between risk groups (*c*-statistic 0.70) in an external validation of a large cohort of CRT patients with long-term follow-up. Moreover, it involves entry of only nine readily available variables. In our model, both AVJA (in patients with permanent AF) and the use of CRT-D were associated with a favourable effect on survival, which is in keeping with other studies.<sup>12,13</sup> A further, important limitation of the SHFM is its practicality, as it involves entry of 25 data fields. In contrast, the CRT risk score herein involves nine variables, which should be readily available to clinicians. In this respect, it is similar to the Euroscore used in cardiac surgery.

## Limitations

The aim of this study was to identify a simple, multi-factorial algorithm that predicts mortality after CRT. While the dataset was

large, data collection cannot be compared with that of randomized clinical trials. As is the case with long-term observational studies of real-world practice, both indications to CRT and CRT technology changed from 1999 to 2012. Admittedly, baseline renal function and natriuretic peptides could add value to the predictive model, but these were not included into the main model because of missing data in more than 25% of cases. However we also reanalysed a subgroup of patients presenting baseline renal function data; even in this subgroup of patients both the predicted and the validated survival curves remained perfectly superimposed, thus reinforcing the goodness of the predictive model.

In addition, we have not considered changes in pharmacological therapy throughout the follow-up period. Notwithstanding, our model provided a reliable prediction of both total and cardiovascular survival. An important distinction between the VALID-CRT score and other scores<sup>31–34</sup> is that it comprises variables that are only available after implantation (e.g. device type). This is likely to amount to a selection bias. As we have not assessed the score in a control group not undergoing CRT, this score does not address the relative benefits of CRT and, therefore, should not be used for patient selection.

## Conclusions

The VALID-CRT risk score is a simple, multifactorial risk-stratification tool for patients implanted with CRT. Our external validation involved prospective data collection in the 'real-world' clinical practice of 72 European centres. The score

proved to be reliably predictive of both total and cardiovascular mortality for up to 6 years of follow-up. In terms of clinical application, this score should not be used in patient selection but rather, for risk stratification following implantation of a CRT device. Accordingly, patients with a high CRT risk score might require more intensive follow-up or alternative and more aggressive therapy than those with a low score. The model is freely available online (<http://www.validcrt.com>) and in iPhone and Android mobile phone applications.

## Supplementary Information

Additional Supporting Information may be found in the online version of this article:

**FigureS1.** Observed and mean overall survival in the second model including the sub-group of patients with creatinine data.

**TableS1.** Observed and mean overall survival in the second model including the sub-group of patients with creatinine data.

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